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EDITORIAL COMMENT

Meta-Analysis of MACE in MI

What's the MO?*

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Since the early days in research on myocardial infarction (MI), it has been recognized that MI size, whether determined by anatomic, electrocardiographic, enzymatic, or imaging methods, and post-MI adverse left ventricular (LV) remodeling are important determinants of early and late major myocardial adverse cardiac events (MACE). In studies of myocardial reperfusion, both in experimental models and in patients, the realization that reperfusion injury could exacerbate the effects of MI also came to the fore early on, and the role of microvascular obstruction (MO) consequent to reperfusion injury has been extensively recognized. The potential role of cardiac magnetic resonance (CMR) for depiction and evaluation of MI using gadolinium contrast became apparent as early as the late 1980s in work from Willerson's group (1), although the potential relevance of CMR in coronary disease was really not appreciated until the contributions of Pohost and colleagues (2) on quantitation of ventricular size and function in the early 1990s. Work on the role of MO in MI in the late '90s contributions of Wu, Lima, and Kim at Hopkins (3–5), followed by development of definitive methods for quantitation of MI size and transmural extent with CMR by Kim, Judd, and Simonetti (5) at Northwestern and Siemens, has made CMR the definitive technique for infarct sizing and detection of MO in vivo. More recently, CMR has provided means for pixel-level quantitation of myocardial perfusion and reliable detection of myocardial edema as a result of reversible injury in the noninfarcted portion of the risk region, so that the risk region and myocardial salvage by reperfusion can be quantitated. In addition, identification and quantitation of intramyocardial hemorrhage (IMH) as a component of reperfusion injury, closely related to MO, has more recently come to the fore. However, as is often the case, the interplay and importance of many closely related MI variables, including infarct size, the effectiveness and timing of reperfusion, severity and extent of reperfusion injury, MO, IMH, post-MI LV remodeling, and extent of coronary disease have left it unclear which are the strongest correlates and potential prognostic indicators of post-MI MACE, including cardiac death and adverse post-MI LV remodeling, and how best they should relate to therapeutic decision making. To complicate clinical matters further, CMR, still the most robust method for infarct sizing, detection of MO, and evaluation of IMH, myocardial salvage by reperfusion, and post-MI LV remodeling, is also the least widely available, particularly in the United States, as well as the most intricate and costly of cardiac imaging technologies and has been affected greatly by turf wars between radiologists and cardiologists. Consequently, use of CMR for evaluation of MI has been more widely applied in European centers, as a result in all likelihood of greater centralization of costly technology and of reperfusion therapy for MI, but its use has been limited in the United States.

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This issue of *iJACC* contains 2 valiant efforts to unravel the conundrum with regard to the relative prognostic associations of various CMR findings in MI. The answers obtained are very helpful, but many important questions remain unanswered.

Hamirani et al. (6) at the University of Virginia have performed a conventional meta-analysis starting with some 33 studies bearing on MO and LV remodeling and 18 addressing MO and MACE. Because CMR methods for assessment of MO varied widely and were evolving over the long time span (1998 to 2014) represented by these studies, they separately considered early post-contrast MO

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imaging, either during first-pass perfusion imaging or immediately thereafter, and late MO imaging at the time of conventional CMR delayed-enhancement imaging for sizing infarction. Because many reports lacked critical components of the data sought, in the end, they evaluated results on 698 patients in 10 studies for early MO in relationship to MACE, 2,132 patients in 7 studies for late MO/MACE, and 631 patients in 9 studies for late MO/remodeling.

By contrast, van Kranenburg et al. (7), writing for a consortium including Dutch, German, French, Spanish, Norwegian, Austrian, and U.S. sites, was able to obtain, combine, and uniformly re-evaluate the detailed individual data on 1,025 patients with ST-segment elevation MI previously reported in 8 published studies—what might be termed a revisionist meta-analysis. They have focused exclusively on late MO, MACE, infarct size, and early post-MI LV size and function.

In general, the results are quite concordant. Late MO was found in >50% of patients in both studies, whereas the MACE risk of MO was more than 4-fold (hazard ratio $[HR]_1$: 4.3 [95% confidence interval (CI): 2.19 to 8.43] vs. HR_2: 4.68 [95% CI: 2.86 to 7.66]) unadjusted for covariates (6,7). After multivariate adjustment, both studies supported the independent effect of MO on MACE, which could be most rigorously and consistently defined by van Kranenburg et al. (7) (MACE adjusted HR: 3.74 [95% CI: 2.21 to 6.34]) considering age, diabetes, multivessel disease, Thrombolysis In Myocardial Infarction flow grade post-PCI, LV ejection fraction (EF), infarct size as %LV mass, and LV end-diastolic volume index. By contrast, infarct size per se was less powerful and not significantly associated with MACE after multivariate adjustment. In the Virginia study (6), early and late MO were also closely associated, as expected, as were late MO and IMH. Late MO was a much stronger correlate of MACE than early MO but did not consistently add power to infarct size for late remodeling among individual studies evaluated.

These analyses are very useful and certainly advance the field, although the limitations of the available data for each, the potential for recruitment bias, and the evolving status of reperfusion, patient management, and CMR over the time periods covered are important limitations. However, the general state of our understanding of CMR findings in MI, in relation to outcomes of MI and post-MI remodeling still points to important questions for which we have no answers. First, on a practical level, after more than 40 years of research on reperfusion injury and its prevention in both surgical myocardial preservation and clinical management of MI, effective, widely accepted approaches to the problem in MI have not yet developed. Although remote ischemic preconditioning, administration of cyclosporine, hypothermia, and other emerging modalities seem promising, much further work needs to be done. Secondly, although it is clear that CMR offers valuable tools for assessment of myocardial damage and its consequences in MI, a compelling case for routine clinical use of CMR is lacking, absent the means to use the results to make therapeutic choices that improve outcomes. Unfortunately, this applies to assessment of LV size and function, as well as tissue composition and perfusion parameters, despite CMR's greater reproducibility of LV volumes and EF. After all, the surviving binary treatment guidelines based on EF were derived from other imaging methods that do not consistently agree closely with CMR in the same patient. Indeed, reports from a number of centers have demonstrated relatively weak correlations between CMR EF and echocardiography or planar multigated acquisition EF and sizable proportions of attribution errors for echocardiography or multigated acquisition assessment of binary EF cutpoints between 30% and 40% when CMR EF is used as a reference standard. Thus, additional large-scale trials on the basis of CMR would be required to rigorously define the role of CMR EF in even well-established therapeutic choices. Lastly, a much better understanding of the mechanisms that determine the roles of intramyocardial hemorrhage and MO in adverse post-MI LV remodeling and the effects of MO on MACE is badly needed and cannot be accomplished with a continued stream of relatively small descriptive studies, bridged by meta-analysis. Rather, much larger-scale, closely coordinated international research efforts on MI incorporating CMR and evaluating potential therapeutic interventions, as well as the funding to support them, are needed. After all, although death rates from coronary disease in developed Western nations reportedly declined to an extraordinary degree in the late 20th century (up to 50% to 80%) with treatment advances accounting for anywhere from one-quarter to one-half of the reductions in various reports, declines have reportedly slowed, coronary disease remains the leading cause of death throughout the world, and its rapidly expanding impact in large populations in low- and middle-income countries hardly augurs well for the future.

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